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ORIGINAL RESEARCH

Correlation Between Vancomycin Trough Concentrations and C-Reactive Protein in Neonates: A Retrospective Observational Study from a Tertiary Hospital in China

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Background: Low initial trough concentrations of vancomycin (TCV) are prevalent among neonatal patients receiving this medication. Prior research has identified significant correlations between initial TCV and various clinical parameters, including postnatal age, gestational age, body weight, estimated glomerular filtration rate (eGFR), and serum albumin levels. However, few studies have addressed the relationship between C-reactive protein (CRP) and initial TCV in neonates. This study aimed to explore the correlation between CRP and initial TCV in a Chinese neonatal population.

Methods: A retrospective observational study was conducted on neonates who received intravenous vancomycin at Northwest Women's and Children's Hospital, China, from October 2018 to December 2023. Clinical characteristics and laboratory data were extracted from medical records, focusing on data obtained within 24 hours prior to the first vancomycin administration. The primary outcomes measured were CRP levels and initial TCV.

Results: A total of 112 neonates with available therapeutic drug monitoring (TDM) data for intravenous vancomycin treatment were included. After adjusting for potential confounders, a non-linear relationship between CRP and initial TCV was identified, with an inflection point at 88.28 mg/L. The effect sizes and corresponding confidence intervals for the regions below and above this inflection point were 0.036 (95% CI: −0.005 to 0.078) and −0.084 (95% CI: −0.142 to −0.027), respectively.

Conclusion: A non-linear relationship between CRP and initial TCV was identified, with a negative correlation when CRP levels exceed 88.28 mg/L.

Keywords: C-reactive protein, vancomycin, neonate, correlation analysis

Introduction

Vancomycin, a glycopeptide antibiotic, is frequently utilized in treating neonatal infections caused by pathogens such as coagulase-negative staphylococci (CoNS), methicillin-resistant Staphylococcus aureus (MRSA), and enterococci.[1,2] However, there is no consensus on the optimal vancomycin dosing for neonates. This is due to their higher body water content, lower protein binding, increased free drug fraction, and reduced renal clearance, which create pharmacokinetic and pharmacodynamic differences from adults.[3]

The 2020 guidelines issued by the Infectious Diseases Society of America (IDSA) seek to determine the most efficacious pharmacokinetic/pharmacodynamic (PK/PD) parameters for vancomycin therapy.[4] In adult patients, an area under the 24-hour concentration-time curve (AUC24) to minimum inhibitory concentration (MIC) ratio exceeding 400 is regarded as the optimal predictor of therapeutic efficacy. Nonetheless, in neonatal clinical practice, serum trough concentrations are frequently employed as a surrogate for the AUC24/MIC ratio, owing to the constraints of limited blood volume and the complexities involved in accurately estimating AUC24.

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Current guidelines recommend vancomycin trough levels of 5–15 μg/mL for newborns, based on adult data not yet validated for neonates.[5] Research highlights that achieving these levels is vital for effectiveness, with 10–11 mg/L ensuring over 90% of neonates reach the AUC 400 target.[6] Early attainment of these levels is linked to higher infection cure rates. Initial trough concentrations of vancomycin (TCV) have been found to correlate with postnatal age, gestational age, body weight, estimated glomerular filtration rate (eGFR), and serum albumin levels.[7] Recent findings suggest that elevated C-reactive protein (CRP) levels, regardless of kidney function, may be a risk factor for reduced vancomycin concentrations.[8] However, Isoda et al found that high initial CRP levels independently predict an increased vancomycin concentration/dose ratio.[9] Whether the results of these two studies apply to the neonatal population remains unknown.

In patients with severe infection, the host's response to bacterial toxins leads to the release of endogenous mediators that increase capillary permeability, induce edema formation, and cause vasodilation and hypotension, resulting in various pathophysiological changes. CRP, an acute phase protein synthesized in the liver and present in the blood, is a sensitive marker of systemic inflammation.[10] Higher CRP levels may indicate that neonates are experiencing more severe infections, which can enhance the exudation of hydrophilic vancomycin from blood vessels due to increased vascular permeability. This exudation results in a larger volume of distribution for vancomycin and consequently reduces its plasma concentration.[11–13]

Based on the existing research findings, there is a correlation between CRP and TCV, but it remains unclear whether this correlation also exists in the neonatal population. This retrospective study investigates the correlation between CRP levels and initial TCV by analyzing specific demographic and clinical data from neonates treated with vancomycin.

Methods

Study Subjects

This retrospective observational study was carried out at Northwest Women's and Children's Hospital in China. The study included patients who received vancomycin treatment between October 2018 and December 2023, and who were admitted to either the neonatal general ward or the neonatal intensive care unit. Participants were excluded from the study if they did not have available vancomycin concentration data, if their medical records were incomplete, if they were administered vancomycin beyond the first 30 days of life, or if their treatment ended due to death.

From the medical records, we collected the data on age, gestational age, sex, height, body weight, infection type, and vancomycin dose. The timing for the collection of laboratory data was within 24 hours prior to the commencement of vancomycin administration, including serum vancomycin concentration, white blood cell count (WBC), hemoglobin, platelet, urea, serum creatinine (SCr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), and albumin (ALB) levels. The eGFR was calculated using Schwartz's formula: $eGFR(mL/min/1.73m^2) = k \times Height(cm) \div Scr(mg/dL)$, k = 0.45 for infants, k = 0.33 in premature infants.[14]

Vancomycin was administered intravenously and the dosage was based on the hospital administration guidelines developed by national pediatric dosing guidelines.[15] The dosage regimen used in this study is presented in Table 1.

Table 1 Vancomycin Dosing Regimen

Gestational Age (Week)	Age (Day)	Single Dose (mg/kg)	Dose Interval (Hour)
≤29	0~14		24
	> 14		12
30~36	0~14	Common infection dose: 10 mg/kg;	12
	> 14		8
37~44	0~7	Severe infection dose: 15 mg/kg	12
	> 7		8
>45			6

Initial TCV Assays

Initial trough blood samples were collected 30 minutes before the fourth dose of vancomycin infusion. Vancomycin blood concentrations were quantified using an enzyme-multiplied immunoassay technique (Emit ® 2000; SIEMENS, Munich, Germany).

Ethical Considerations

This study was conducted in compliance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Northwest Women's and Children's Hospital (No. 2023010). Due to the retrospective nature of the study, which involved anonymous data and no intervention, informed consent was waived by the Ethics Committee.

Statistical Analysis

We presented continuous variables as mean (standard deviation) for data following a Gaussian distribution or median (range) for data with a skewed distribution. Categorical variables are expressed as counts with their respective proportions. To identify differences among various initial TCVs of vancomycin (a binary variable), we used several statistical tests for our analysis. For categorical variables, we employed the $\chi 2$ test. For data that was normally distributed, we used the One-Way ANOVA test. And for skewed data, we relied on the Kruskal–Wallis *H*-test. To explore the correlation between CRP (C-reactive protein) and initial TCV (trough concentrations of vancomycin), we developed three distinct models using both univariate and multivariate linear regression. These included: a non-adjusted model (with no covariates), a minimally adjusted model (adjusting only for sociodemographic variables), and a fully adjusted model (including all covariates listed in Table 1). We documented effect sizes along with their 95% confidence intervals. To account for potential non-linearity between CRP and initial TCV, we used a Generalized Additive Model (GAM) and smooth curve fitting with penalized splines. Additionally, a two-piecewise linear regression model was employed to further elucidate the non-linearity. Since BMI, daily vancomycin dose, ALB, and eGFR are all significant factors affecting initial TCV, we adjusted for these important influencing factors in the non-linear fitting process between CRP and initial TCV. To test the robustness of our findings, a sensitivity analysis was conducted. CRP was categorized based on quartiles, and the P for trend was calculated to corroborate the results obtained with CRP as a continuous variable and to investigate the possibility of non-linearity. Statistical modeling was conducted using the software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). P values of less than 0.05 (two-tailed) were considered to indicate statistical significance.

Results

Baseline Characteristics of Participants

In this analysis, out of a total of 268 participants, 156 were deemed ineligible for the study, as depicted in Figure 1. The exclusion criteria for these 156 individuals were as follows: 90 lacked continuous therapeutic drug monitoring of vancomycin (TCV), 35 had incomplete medical documentation, 25 were treated with vancomycin for over 30 days, and 6 died during the treatment. The clinical profiles and laboratory findings of the 112 eligible patients are detailed in Table 2.

The average age of the study cohort was 16.12 ± 7.06 days, of which 62.5% were male, and 37.5% were female. Among the 112 enrolled neonates, 71 (69.39%) were preterm: 15 extremely preterm (<28 weeks), 42 very preterm (28–31 weeks), 7 moderate preterm (32–33 weeks) and 7 late preterm (34–36 weeks); the remaining 41 (36.61%) were full-term. The median level of CRP is 20.46 mg/L, and the median level of initial TCV is 9.35 μg/mL. We divided patients into subgroups use the initial TCV tertiles (<7.4, 7.4–11.4, >11.5 μg/mL). Analysis of these subgroups revealed that neonates with higher initial TCV levels were significantly more likely to be male ($P<0.05$). Additionally, these neonates received a significantly higher daily dose of vancomycin ($P<0.001$) and exhibited a significantly higher eGFR ($P<0.05$). There were no significant differences in age, gestational age, height, weight, or treatment outcomes ($P>0.05$).

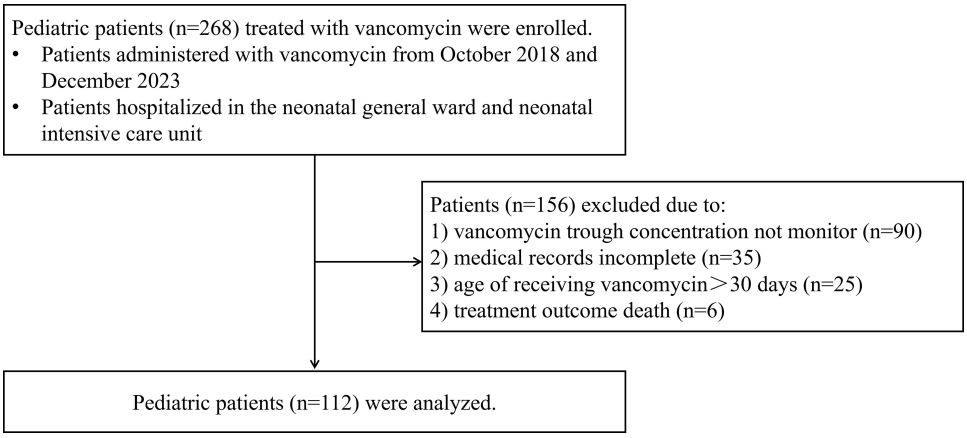

Figure 1 Flowchart of the study population.

In the laboratory data analysis, neonates exhibiting higher initial TCV tended to have lower median CRP levels, although this correlation was not statistically significant. Additionally, no significant statistical differences were observed in the levels of WBC, Hemoglobin, Platelets, ALB, ALT, AST, Urea, and SCr across the various initial TCV groups.

Univariate Analysis of Initial TCV

The outcomes of the univariate analysis are delineated in Table 3. It was demonstrated that vancomycin daily dose correlated positively with higher initial TCV in neonates (β = 0.2, 95% CI: 0.11 to 0.3, P < 0.01). Moreover, it was observed that sex, gestational age, BMI, WBC, CRP, hemoglobin, platelet, ALB, ALT, AST, urea, eGFR, and treatment outcome were not significantly associated with the initial TCV in neonates.

The Relationship Between CRP and Initial TCV

A multiple linear regression model was used to evaluate the associations between CRP (C-reactive protein) and Initial TCV (trough concentrations of vancomycin), including non-adjusted and adjusted models, which are shown in Table 4. In the crude model, CRP showed no correlation with Initial TCV (β= −0.002, 95% CI: − 0.03 to 0.02, P= 0.90). In model I (adjusted sex, age, BMI, weight, height), we did not detect any connection in a minimally adjusted model (β= −0.003, 95% CI:-0.03 to 0.02, P= 0.81). After adjusting for other covariates (sex, age, BMI, weight, height, vancomycin daily dose, WBC, hemoglobin, platelet, ALB, ALT, AST, urea, eGFR, treatment outcome), the effect size showed an obvious change (β= −0.01, 95% CI: −0.05 to 0.01, P= 0.33). For the purpose of sensitivity analysis, we also handled CRP as a categorical variable (quartile) and found the same trend (p for the trend was 0.11).

The Analyses of Non-Linear Relationship

In this study, as CRP is a continuous variable, we also used the generalized additive model (GAM) to judge if it existed a non-linear relationship between CRP and initial TCV. The smooth curve through the analysis of GAM showed that CRP had a non-linear relationship with initial TCV (adjusted for BMI, vancomycin daily dose, ALB, and eGFR) (Figure 2). By using a two-piecewise linear regression model, we calculated that the P for the loglikelihood ratio is less than 0.005, and the inflection point was 88.28 (Table 5). On the left of the inflection point, no association was found between CRP and initial TCV (β= 0.036, 95% CI: −0.005 to 0.078, P= 0.092). However, we also observed a negative relationship between CRP and initial TCV on the right side of the inflection point (−0.084, −0.142 to −0.027, 0.005).

Discussion

Vancomycin, a glycopeptide antibacterial agent, exerts its potent sterilizing action by inhibiting the synthesis of the cell wall in sensitive bacteria, altering the permeability of bacterial cell membranes, and impeding RNA synthesis within the bacterial cytoplasm. In the human body, vancomycin is not metabolized by the liver and is primarily eliminated through

Table 2 Baseline Characteristics of Participants

Characteristics	Total	Initial TCV, μg/mL			P Value
		T1 (<7.4)	T2 (7.4–11.4)	T3 (>11.4)	
N	112	36	38	38	
Preterm, N (%)					0.205
Extremely preterm (<28weeks gestation)	15 (13.39%)	7 (19.44%)	7 (18.42%)	1 (2.63%)	
Very preterm (28–31 weeks gestation)	42 (37.50%)	14 (38.89%)	13 (34.21%)	15 (39.47%)	
Moderate preterm (32–33 weeks gestation)	7 (6.25%)	1 (2.78%)	2 (5.26%)	4 (10.53%)	
Late preterm (34–36 weeks gestation)	7 (6.25%)	0 (0.00%)	4 (10.53%)	3 (7.89%)	
Full-term (≧37weeks gestation)	41 (36.61%)	14 (38.89%)	12 (31.58%)	15 (39.47%)	
Sex, N (%)					0.010
Male	70 (62.50%)	20 (55.56%)	19 (50.00%)	31 (81.58%)	
Female	42 (37.50%)	16 (44.44%)	19 (50.00%)	7 (18.42%)	
Age, Mean (SD), day	16.12 (7.06)	16.64 (6.41)	15.68 (7.45)	16.08 (7.40)	0.846
Gestational Age, Mean (SD), day	235.50 (35.11)	233.64 (38.65)	232.32 (36.62)	240.45 (30.09)	0.562
Height, Mean (SD), cm	42.36 (7.49)	41.39 (7.74)	41.09 (7.47)	44.55 (6.95)	0.083
Weight, Median (Q1-Q3), kg	1.60 (1.16–3.25)	1.40 (1.18–3.22)	1.80 (1.30–2.94)	2.14 (1.62–3.29)	0.359
Vancomycin Daily Dose, Mean(SD), mg/kg	32.11 (11.49)	25.14 (10.32)	32.18 (10.34)	38.64 (9.88)	<0.001
WBC, Mean (SD), $\times 10^9$/L	11.89 (6.31)	11.56 (6.29)	12.41 (5.92)	11.69 (6.82)	0.824
CRP, Median (Q1-Q3), mg/L	20.46 (4.32–44.36)	26.02 (6.51–45.23)	19.84 (4.29–38.14)	13.88 (3.60–48.80)	0.414
Hemoglobin, Mean (SD), g/L	134.28 (26.55)	133.94 (19.70)	139.21 (24.36)	129.66 (33.28)	0.294
Platelet, Median (Q1-Q3), $\times 10^9$/L	202.00 (84.00–329.50)	157.50 (56.75–342.00)	254.00 (159.75–332.50)	189.50 (81.75–261.75)	0.471
ALB, Mean (SD), g/L	29.27 (4.43)	29.49 (4.20)	29.83 (5.26)	28.52 (3.72)	0.422
ALT, Median (Q1-Q3), U/L	7.57 (5.24–14.77)	7.90 (5.42–16.95)	6.27 (4.80–13.80)	7.56 (5.76–14.57)	0.488
AST, Median (Q1-Q3), U/L	29.73 (21.12–37.92)	30.31 (23.23–41.56)	26.82 (20.41–34.34)	30.50 (21.00–38.98)	0.295
Urea, Median (Q1-Q3), mmol/L	4.06 (2.60–5.78)	4.05 (2.90–6.29)	3.34 (2.28–5.61)	4.47 (3.50–5.79)	0.751
SCr, Mean (SD), μmol/L	38.24 (17.65)	38.30 (15.33)	36.81 (14.45)	39.57 (22.24)	0.797
eGFR, Median (Q1-Q3), mL/min/1.73m^2	38.56 (25.20–60.56)	37.86 (25.10–80.63)	35.91 (23.94–50.40)	48.55 (29.92–71.39)	0.023
Treatment outcome, N (%)					0.880
Cure	30 (26.79%)	9 (25.00%)	12 (31.58%)	9 (23.68%)	
Effect	77 (68.75%)	25 (69.44%)	24 (63.16%)	28 (73.68%)	
Failure	5 (4.46%)	2 (5.56%)	2 (5.26%)	1 (2.63%)	

Abbreviations: TCV, trough concentrations of vancomycin; WBC, white blood cell; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

renal excretion. In premature neonates, the renal clearance rate of vancomycin ranges from 0.3 to 1.7 mL/kg/min.[16] Under conditions of normal renal function, vancomycin exhibits a protein binding rate of approximately 55%. In contrast, newborns possess immature renal metabolic capabilities, which result in reduced kidney clearance and a subsequent alteration of vancomycin's in vivo pharmacokinetics. Furthermore, the pathological state of infection in neonates tends to induce additional variations in the pharmacokinetic profile of vancomycin.[8]

In this present study, we used linear regression model and GAM to elucidate the relationship between CRP (C-reactive protein) and initial TCV (trough concentrations of vancomycin) among neonates. As is shown in crude model and minimally adjusted model, CRP was not associated with initial TCV (crude model: β= −0.002, 95% CI: −0.03 to 0.02, P= 0.90; model 1: β= −0.003, 95% CI: −0.03 to 0.02, P= 0.81). However, after adjusting for fully covariates, the effect size showed an obvious change (β= −0.01, 95% CI: −0.05 to 0.01, P= 0.33), even if the 95% confidence interval did not change. When we handled CRP as a categorical variable, the same trend was observed, except that CRP Q4 showed a correlation with the initial TCV in Model II. In addition, the results of GAM and a two-segment linear regression model showed that the relationship between CRP and initial TCV was non-linear, and the correlations between CRP and initial TCV were different on the left and right sides of the inflection point (CRP = 88.28). CRP, as assessed at baseline, was not statistically significant on the left side of the inflection point, but CRP was negatively correlated with initial TCV above the inflection point (β= −0.084, 95% CI: −0.142 to −0.027, P= 0.005).

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Table 3 The Result of Univariate Analysis of Initial TCV

	Statistics	Effect Size (β)	P Value
Sex			
Male	70 (62.50%)	ref	
Female	42 (37.50%)	−1.10 (−3.45, 1.24)	0.359
Gestational Age	235.50 ± 35.11	0.01 (−0.02, 0.05)	0.393
Vancomycin Daily Dose	32.11 ± 11.49	0.20 (0.11, 0.30)	<0.01
WBC	11.89 ± 6.31	−0.01 (−0.19, 0.17)	0.888
CRP	36.75 ± 46.72	−0.002 (−0.03, 0.02)	0.902
Hemoglobin	134.28 ± 26.55	0.003 (−0.04, 0.05)	0.903
Platelet	225.39 ± 170.02	−0.001 (−0.01, 0.01)	0.736
ALB	29.27 ± 4.43	−0.18 (−0.44, 0.08)	0.177
ALT	11.90 ± 14.90	−0.002 (−0.08, 0.08)	0.958
AST	35.57 ± 31.85	0.001 (−0.04, 0.04)	0.949
Urea	9.86 ± 24.72	0.01 (−0.03, 0.06)	0.563
eGFR	49.55 ± 35.45	−0.002 (−0.03, 0.03)	0.904
Treatment outcome			
Cure	30 (26.79%)	ref	
Effect	77 (68.75%)	0.10 (−2.51, 2.71)	0.939
Failure	5 (4.46%)	−1.48 (−7.33, 4.38)	0.622

Abbreviations: TCV, trough concentrations of vancomycin; WBC, white blood cell; CRP, C-reactive protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate.

Table 4 Relationship Between CRP and Initial TCV in Different Models of Multivariate Analysis

Variable	Crude Model (β, 95% CI, P)	Model I (β, 95% CI, P)	Model II (β, 95% CI, P)
CRP	−0.002 (−0.03, 0.02) 0.90	−0.003 (−0.03, 0.02) 0.81	−0.01 (−0.04, 0.01) 0.33
CRP quartile			
Q1	Ref	Ref	Ref
Q2	0.47 (−2.74, 3.67) 0.78	1.07 (−2.27, 4.42) 0.53	1.60 (−1.59, 4.79) 0.33
Q3	−0.80 (−4.01, 2.40) 0.62	−0.12 (−3.48, 3.25) 0.95	1.54 (−2.03, 5.11) 0.40
Q4	2.23 (−0.97, 5.44) 0.17	2.57 (−0.76, 5.91) 0.13	9.74 (3.49, 15.98) <0.01
P for trend	0.30	0.22	0.11

Note: Crude model: No variables are adjusted. Model I: Adjusted sex, age, BMI, weight, height. Model II: Adjusted sex, age, BMI, weight, height, vancomycin daily dose, WBC, hemoglobin, platelet, ALB, ALT, AST, urea, eGFR and treatment outcome.
Abbreviations: TCV, trough concentrations of vancomycin; CRP, C-reactive protein; CI, Confidence interval; Ref, Reference.

We conducted a PubMed search using the keywords "C reactive protein", "concentration of vancomycin", and "neonate" simultaneously. Five scientific papers were retrieved from the database as of the end of August 2024.[1,17–20] All of these studies have indicated an association between CRP levels and vancomycin concentrations in neonates. However, none have addressed the link between CRP and initial TCV. To our knowledge, this investigation is the first to explore the relationship between CRP and initial TCV in neonatal populations. The mechanisms behind this phenomenon remain unclear.

Elevated CRP, a widely accepted surrogate of systemic inflammation, may perturb vancomycin pharmacokinetics in neonates through two inter-related mechanisms.[8] First, inflammatory cascades may increase vascular permeability by disrupting endothelial integrity, thereby facilitating the egress of hydrophilic vancomycin from the intravascular to the interstitial compartment and expanding its volume of distribution. Second, sepsis-associated cytokines (IL-1β, IL-6, TNF-α) may up-regulate active tubular secretion and glomerular hyperfiltration, collectively manifesting as augmented renal clearance (ARC) that shortens vancomycin half-life and lowers trough concentrations. In this study, neonates with higher initial TCV levels received significantly higher daily doses of vancomycin (P<0.05) and had significantly higher

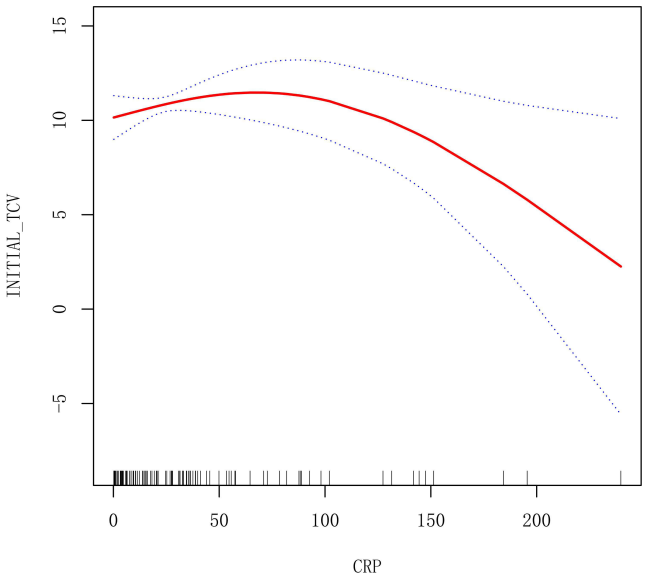

Figure 2 Association between CRP and initial TCV in neonates. A non-linear association between CRP and initial TCV was found in a generalized additive model (GAM). Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. All adjusted for BMI, daily vancomycin dose, ALB, and eGFR.

eGFR (P<0.05). To explain the divergent relationship between higher TCV levels and higher eGFR, a nonlinear analysis of TCV and eGFR was conducted in this study (Supplementary Figure 1), revealing no association between TCV and eGFR before and after adjusting for daily dose. This paradoxical relationship may be related to the small sample size.

In present study, after the curve fitting of CRP and initial TCV, there is an obvious nonlinear characteristic and an obvious breakpoint. In the threshold effect analysis, after adjusting BMI, daily dose of vancomycin, ALB and eGFR, the break point was 88.28, and the log-likelihood ratio test was 0.005 (P < 0.05). When CRP was less than 88.28, there was no correlation between CRP and initial TCV. When CRP was more than 88.28, CRP was negatively correlated with the value of initial TCV. For every 10 units of CRP increased, the initial TCV decreased by 0.84μg / mL. This finding can provide some reference for the formulation of the initial dose and adjustment dose of vancomycin. CRP plays a significant role in inflammation and immune responses. It not only reflects the presence of inflammation but may also directly participate in the inflammatory process and alterations in vascular endothelial function. Around the specific value of 88.28 mg/L, CRP may reach a biological threshold, beyond which its impact on endothelial cell function and the promotion of inflammatory responses may significantly intensify, leading to nonlinear changes in the relationship with TCV. Our findings are consistent with some studies, with multiple studies indicating that CRP levels in patients with severe infections are often above 50–100 mg/L. In patients with sepsis, the average CRP value is 85 mg/L,[21] in severe

Table 5 Two-Piecewise Linear Regression Model to Evaluate Relationship Between CRP and Initial TCV

	Initial TCV (β, 95% CI, P)
Model I	
A straight line effect	−0.011 (−0.037, 0.015) 0.424
Model II	
Inflection point (K)	88.28
< K	0.036 (−0.005, 0.078) 0.092
> K	−0.084 (−0.142, −0.027) 0.005
P for log-likelihood ratio test	0.005

Note: we adjusted BMI, vancomycin daily dose, ALB, and eGFR.
Abbreviations: TCV, trough concentrations of vancomycin; CRP, C-reactive protein; CI, Confidence interval.

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sepsis patients it is 161.8 mg/L,[22] and in septic shock patients it is ≥175.42 mg/L,[23] possibly reflecting varying degrees of inflammatory response. These studies suggest that CRP may indicate a state of change in the host's pathological condition and vancomycin pharmacokinetics around the specific value of 88.28 mg/L. When CRP values are less than 88.28 mg/L, it indicates that the infection is in an acceptable state and vancomycin pharmacokinetics remain stable When CRP values exceed this threshold of 88.28 mg/L, the amount of vancomycin distributed from the bloodstream to tissues increases, and early acute infection-induced renal hyperfunction leads to increased vancomycin filtration, collectively resulting in reduced vancomycin blood concentrations.

We found that the total daily dose of vancomycin is also a key factor affecting the concentration of vancomycin. In the univariate analysis, the total daily dose was significantly correlated with the initial TCV, the effect value β was 0.02 (0.11,0.3), and the P value was < 0.01. In this study, multiple regression analysis was not performed on the total daily dose and the initial TCV, and the total daily dose was only used as a mixed adjustment variable for the multiple regression analysis of CRP and initial TCV. According to the 2020 guidelines for the treatment of MRSA infections in adults and pediatrics by the Infectious Diseases Society of America (IDSA), the recommended dosing range for vancomycin in neonates and infants under 3 months is 10 to 20 mg/kg every 8 to 48 hours.[16] It can be seen from Table 2 that in the initial TCV < 7.4μg / mL group, the average daily total dose was 25.14 mg/kg. Although this dose is within the recommended dose range of IDSA, the initial TCV obtained is low, which may reduce the clinical efficacy of vancomycin or induce drug resistance. The univariate analysis of this study showed that the total daily dose was positively correlated with the initial TCV, and it was recommended to increase the initial TCV by increasing the daily dose of vancomycin.

However, studies have suggested that higher doses of vancomycin could be associated with an increased risk of nephrotoxicity.[24,25] We recognize that when adjusting vancomycin doses to achieve higher TCV, a balance must be struck between therapeutic efficacy and the risk of nephrotoxicity. According to the literature, there is a positive correlation between vancomycin's steady-state trough concentrations and the incidence of acute kidney injury (AKI), particularly when trough concentrations > 15 mg/L, the incidence of vancomycin-associated AKI significantly increases.[6,26,27] In the context of severe infections such as sepsis, the potential for ARC can lead to more rapid elimination of vancomycin, which might necessitate higher doses to achieve therapeutic levels. Although previous studies have suggested that the lower degree of renal maturation in neonates affects the clearance of vancomycin, the aforementioned literature also considers the enhancement of renal clearance induced by severe infections as a factor that cannot be ignored.[28] Therefore, more studies are needed to provide a reference for the dose adjustment of vancomycin. However, the correlation between vancomycin and nephrotoxicity in neonates is currently unclear. Therefore, we suggest that future studies should further explore the optimal dosage of vancomycin in neonates and how to optimize dosing through therapeutic drug monitoring (TDM) to reduce the risk of nephrotoxicity while maintaining efficacy.

In multiple population pharmacokinetic (PPK) studies of vancomycin in premature and term neonates, it has been reported that weight, creatinine clearance, and postnatal weight gain significantly affect vancomycin clearance; weight is the most significant covariate for vancomycin volume of distribution.[7,29,30] Additionally, as the age of neonates increases after birth, their renal function and extracellular fluid volume are also continuously changing, leading to greater interindividual variability, thus there is an urgent need for individualized application of vancomycin in neonates. Although current PPK studies have considered multiple important covariates, The results of population pharmacokinetic studies on vancomycin in the neonatal population remain inconsistent. The correlation between CRP and initial TCV found in this study suggests that pre-medication CRP levels can serve as an important reference covariate for dose adjustment or PPK studies.

Similar studies have been documented in adult populations. A retrospective study conducted in Japan on vancomycin therapy found that CRP concentrations were significantly higher in patients with low vancomycin trough levels compared to those with normal levels, regardless of baseline renal function.[8] This finding aligns with our observations. In contrast, a multicenter population pharmacokinetic analysis from Saudi Arabia indicated that elevated CRP concentrations were associated with higher vancomycin trough levels in non-critically ill elderly patients with similar creatinine clearance.[31] This discrepancy likely arises from the exclusion of critically ill individuals, suggesting that the recorded CRP values may not accurately reflect the true inflammatory status at the initiation of vancomycin therapy. While pediatric studies

directly investigating the relationship between CRP levels and vancomycin exposure are limited, significant elevations in CRP typically indicate severe infections in children. A recent study demonstrated that ARC is highly prevalent, with 67% of patients experiencing at least one episode of ARC during a four-day observation period, among critically ill children aged 1 month to 15 years.[32] Furthermore, in a cohort of pediatric patients with suspected sepsis, the presence of ARC was associated with sub-therapeutic initial vancomycin trough concentrations.[33] In comparison to older children and adults, neonates and young infants possess a relatively larger extracellular and total body water compartment, which leads to an increased volume of distribution for hydrophilic agents such as vancomycin, resulting in lower trough concentrations. Although traditional dosing regimens have considered the decreased renal function characteristic of this age group, the recently acknowledged enhancement of vancomycin clearance due to increased renal function has recently been integrated into pediatric pharmacokinetic models.[34]

Our study has a number of strengths. First, we not only use the generalized linear model to evaluate the linear relationship between CRP and initial TCV but also use the generalized additive model to clarify their nonlinear relationship. GAM has obvious advantages in dealing with nonlinear relationships. It can handle nonparametric smoothing and fit regression splines to data. The use of GAM will help us better discover the true relationship between exposure and results. Second, this study is an observational study, including unavoidable potential confounders; therefore, we used strict statistical adjustment to minimize residual confounding. Third, we had the positive finding that CRP was greater than 88.28, and for every 10 unit increase in CRP, initial TCV decreased by 0.84 μg/mL. The clinical value of this finding is that the association of CRP and initial TCV can only be observed when CRP reaches a certain threshold.

There are some limitations in this study. First, this study was a single-center study, which used empirical vancomycin doses for special groups such as neonates, and did not conduct a subgroup study of full-term and preterm neonates. Therefore, the results of this study may not be generalizable to other neonatal populations. Second, this study is a retrospective case-control study, which may lead to incomplete or unavailable data in the records. This could lead to potential biases in our study. To mitigate the impact of these limitations, we adjusted for known factors affecting vancomycin trough concentrations as much as possible in our analysis. Furthermore, we were unable to control for all potential confounding factors, which may affect the interpretation of our study's results. Third, the sample size of this study is small, so the risk cannot be accurately predicted. Despite the limitations, our study provides important insights into the pharmacokinetics of vancomycin in neonates, and our results are consistent with the existing literature, which adds robustness to our findings. Finally, this study only analyzed the relationship between CRP and initial TCV before treatment, and did not evaluate the effectiveness of treatment and microbiological results. Future studies should aim to more accurately assess the relationship between CRP and TCV through prospective study designs, better control data collection to reduce retrospective bias, and expand to multicenter studies to increase sample size, thereby enhancing the reliability and generalizability of the findings. Future research should also attempt to link TCV and CRP levels to clinical outcomes such as resolution of infection, nephrotoxicity, or other adverse events, to realize the clinical significance of adjusting vancomycin doses based on CRP levels, while also reducing the risk of nephrotoxicity according to CRP levels, finding a balance between the efficacy and safety of vancomycin treatment in the neonatal population.

Conclusion

This study investigates the correlation between CRP and initial TCV in neonatal population. CRP level may be one of the risk factors associated with the decrease of initial TCV in neonatal patients. When CRP levels exceed a specified threshold (eg, 88.28 mg/L), a notable inverse correlation with initial TCV is observed. Traditionally, it has been hypothesized that severe illness may impair renal function, leading clinicians to administer reduced vancomycin doses, which consequently result in sub-therapeutic plasma levels. In cases where CRP exceeds the threshold, clinicians may consider increasing the dosage to achieve therapeutic levels. However, due to neonates' immature renal clearance, any dosage adjustments should be accompanied by careful TDM of vancomycin and regular monitoring of renal injury markers to ensure safe, individualized treatment. Future studies should quantify the link between CRP levels and vancomycin dosing to refine dosing regimens for neonates.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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